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14. ABSTRACT

This Award funded the initiation of a mentored research experience in ovarian cancer biology at the Dana Farber/Harvard Cancer Center. The primary aims, articulated in the Statement of Work, included creating a mechanism to identify and select outstanding postdoctoral fellows who had a commitment to serious multi-year experience in research that was directly related to a topic in or immediately applicable to ovarian cancer. The second aim was to provide a mentored experience for selected fellows. The third aim specified the delivery of feedback to the trainees by mentors and the program PI. The final aim described a rigorous review process for the program. These aims are all being addressed. Of the four senior post doctoral fellows selected to work with Faculty at Harvard Medical School in the fields of oncogenesis, signal transduction, pathology and mouse models and cell biology, one fellow graduated from the program and is successfully transitioning towards an independent academic research career. The vacancy was competed for and filled successfully. A new faculty member with extensive training in biologic models was added to the program to mentor the fellows, who continue to pursue their research productively at 3 different institutions within the Dana Farber/Harvard Cancer Center.

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Final Report for the DOD/OCRP Training Grant

PI Michael Seiden M.D. Ph.D.

This is the Year 3 progress report for the training grant supported through the Ovarian Cancer Research Program mechanism, which in turn is supported by the Department of Defense. A program was funded to support the training of three postdoctoral fellows in research. Below is listed the Statement of Work of the Ovarian Cancer Training Grant at the MGH.

Statement of work

1) Identify and select outstanding postdoctoral fellows for participation in ovarian cancer training program

2) Identify appropriate faculty and mentors for selected postdoctoral fellows

3) Review progress of postdoctoral candidates by Principal Investigator and Executive Committee

4) Review overall Training Program

SOW Aim #1 Identify and select outstanding postdoctoral fellows for participation in ovarian cancer training program

During the third and final year of the program we continued funding for Dr. John Miao and selected two new candidates: Dr. Zhijian Gao and Dr. Deying Xing. In addition prior graduates of the program continued to do well. Dr. Ronny Drapkin graduated from the program and is now an independent faculty member and Assistant Professor of Pathology at the Harvard Medical School in the Division of Molecular Pathology at the Dana Farber Cancer Center. Dr. Zhan returned to China as a faculty member in basic science.

SOW Aim #2 Identify appropriate faculty and mentors for selected postdoctoral fellows

Sandra Orsulic is the mentor for Dr. Xing and Dr. Miao. Dr. Gao was mentored by Dr. Samuel Mok at the Brigham and Women's Hospital and his partner Dr. Beth Garner. Dr. Mok qualifications were listed in the original application and he continues to be a leader in the comprehensive genetic analysis of ovarian cancer.

SOW AIM #3 Review progress of postdoctoral candidates by Principal Investigator and Executive Committee

The principal investigator met several times with all the mentees during the final year of the grant including all the graduates with the exception of Dr. Zhan (now in China). In addition, the graduates continued to attend the monthly Ovarian Cancer Basic Science Seminar that is under

the direction of Dr. Orsulic. All have presented at the seminar series with the exception of Dr. Gao who will likely present in the future.

Publications of all Fellow (2003-2006):

Drapkin Publications during DOD funded support:

1) Drapkin R, Crum CP, Hecht J. Expression of candidate tumor markers in ovarian carcinoma and benign ovary: evidence for a link between epithelial phenotype and neoplasia. *Human Pathology* 2004, 35: 1014-1021.

2) Drapkin R, von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, Hecht J. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Res* 2005; 65: 2162-2169.

Sonja Sale Publications during DOD funded support:

Zhan Publications during DOD funded support:

1) Zhan Y, Fujino A, MacLaughlin DT, Manganaro TF, Szotek PP, Arango NA, Teixeira J, Donahoe PK. Mullerian inhibiting substance regulates its receptor/SMAD signaling and causes mesenchymal transition of the coelomic epithelial cells early in Mullerian duct regression. *Development* 2006, 133(12):2359-69.

John Miao Publications during DOD funded support:

1) Miao J, Wang Z, Provencher H, Muir B, Dahiya S, Carney E, Leong CO, Sgroi DC, Orsulic S. HOXB13 promotes ovarian cancer progression. *Proc Natl Acad Sci USA* 2007, 104(43):17093-8.

Zhijian Gao Publications during DOD funded support:

1) Litkouhi B, Kwong J, Lo C-M, Smedley JG, McClane BA, Aponte M, Gao Z, Sarno JL, Hinners J, Welch JF, Berkowitz RS, Mok SC, Garner EI. Claudin-4 overexpression in epithelial ovarian cancer is associated with hypomethylation and is a potential target for modulation of tight junction barrier function using a C-terminal fragment of Clostridium perfringens enterotoxin. *Neoplasia* 2007, 9(4):304-14.

Deyin Xing Publications during DOD funded support:

1) Xing D, Orsulic S. A mouse model for the molecular characterization of Brca1-associated ovarian carcinoma. *Cancer Research* 2006, 66: 8949-8953.

2) Xing D, Orsulic S. Modeling resistance to pathway-targeted therapy in ovarian cancer. *Cell Cycle* 2005, 4(8):1004-6.

3) Xing D, Orsulic S. A genetically defined mouse ovarian carcinoma model for the molecular characterization of pathway-targeted therapy and tumor resistance. *Proc Natl Acad Sci USA* 2005, 102(19):6936-41.

New Fellow- (2005-)

From 2005-2006 Dr. Zhijian Gao is working on the role of claudin 4 in ovarian cancer with Dr. Samuel Mok and Beth Garner.

Gao's research abstract

Claudin 4 is cellular protein located at intercellular tight junctions. The protein also is a receptor for the C-terminal fragment of Clostridia perfringens enterotoxin. The protein is over expressed in ovarian cancer cell lines and some ovarian tumors. Our studies look to gain a better understanding of claudin 4 expression in ovarian cancer, the prognostic significance of claudin 4 over expression and its mechanisms of over expression within tumor cells. In addition, the studies look to begin to explore how claudin 4 might be used as a therapeutic target in ovarian cancer.

Dr. Deyin Xing

Dr. Xing's research focuses on molecular models of ovarian cancer with Sandra Orsulic.

Abstract

Ovarian cancer results from a series of genetic mutations that in turn drive uncontrolled cell growth, metastasis's, and eventually resistance to standard and molecularly targeted therapies. Using a variety of genetic strategies, mouse epithelial cells can be altered through deletion of tumor suppressor genes or insertion of oncogenes to convert benign ovarian epithelium to malignant epithelium. This work uses a variety of techniques to delete the key tumor suppressors such as p53 and BRCA1 as well as introducing known and novel oncogenes including Myc, Ras, activated AKT, Her-2-neu, and now the Hox genes to explore how these genes cooperate to generate the malignant phenotype.

Evaluation of the mentees:

Dr. Zhijian Gao was hard working and earnest in her efforts. Her command of English needed work and this improved over the course of the year. In addition, she was at times over enthusiastic to move on with second or third tier experiments before the primary experiments had been repeated and thoroughly documented and on several occasions she needed to have her efforts refocused. Nevertheless all thought her efforts were sincere and her desire to be productive very laudatory.

Dr. Deyin Xing was very productive and was felt to be an outstanding collaborator and was developing rapidly towards an independent faculty career. Indeed after his time with Dr. Orsulic he has chosen to obtain further scientific training with Dr. Philip Sharp, a Nobel Laureate, at the

Massachusetts Institute of Technology. It is likely that Dr. Xing will seek an independent faculty position after this postdoctoral training experience.

Dr. John Miao was productive and was a very careful experimentalist and after rapidly improved his presenting skills and broadened his comfort with a wide variety of techniques. He has also decided to obtain further scientific training and is now with Dr. David Louis, Chairman of Pathology at Massachusetts General Hospital. His future career plans after completing his work with Dr. Louis are still undefined.

SOW Aim #4 Review overall Training Program

With the impending expiration of funding through the DOD mechanism a T32 application was submitted to the NCI and then revised applications where submitted in 2005 and 2006. In late 2006, we were informed that the grant had a fundable score and would fund up to five postdoctoral candidates a year. Unfortunately, I served as the PI of the grant and when I accepted the position of President and CEO at Fox Chase Cancer Center the NCI withdrew its offer to fund the grant at Harvard. Nevertheless the program the strong and fundable review of the program at NCI was based, in part, on the success of the DOD program.